REMARKS

Claims 20, 24-26, 31-33 and 36-53 are pending in the application.

Rejection of Claims 20, 24-26, 31-53 Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner has rejected claims 20, 24-26, 31-53 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully submit that only certain of these claims (claims 20, 24-26, 31-33 and 36-53) are currently pending in the application, and request correction on the record. Applicants traverse this rejection.

Applicants respectfully remind the Examiner of the standard for establishing therapeutic utility of biotechnological inventions under 35 U.S.C. § 112, first paragraph, as set forth by the Federal Circuit in *In re Brana*, 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). In that case, the Federal Circuit held that a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, must be taken as in compliance with the enabling requirement of the first paragraph of §112 ***unless there is reason to doubt the objective truth of the statements which must be relied on for enabling support***. The PTO thus has the initial burden of challenging a presumptively correct assertion of utility. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See *In re Bundy*, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (CCPA 1981).

Here, the Examiner has failed to establish that one of ordinary skill in the art would doubt the objective truth of Applicants' statements related to use of soluble LTβR agents for treatment of follicular lymphoma. The evidence upon which the Examiner has relied – Ponzio *et al.* and U.S. Patent No. 5,925,351 ("the '351 patent"; one inventor common with the instant application) – would not convince one of ordinary skill in the art reasonably to doubt Applicants' asserted use of soluble LTβR agents for treating follicular lymphoma, particularly in view of Applicants' *in vivo* experiments demonstrating treatment of tumors in an animal model following administration of soluble LTβR. Applicants therefore submit that the present disclosure fully

satisfies the enablement standard set forth in *In re Brana* in that it provides more than a sufficient teaching of how to make and use the claimed methods.

Applicants performed the LTβR treatment experiments of the present application in a mouse model of lymphoid tissue tumor (*e.g.*, follicular lymphoma, B cell lymphoma) that featured transplantation of reticular cell sarcoma (RCS) tumors into SJL mice susceptible to such tumors. As described in the present application, Applicants observed a two- to ten-fold reduction in lymph node weight as a result of various regimens of LTβR-Ig treatment in this art-recognized model of lymphoid tumor/follicular lymphoma. In view of these dramatic results in an animal model of lymphoid tissue tumor, one of ordinary skill in the art would not have reasonably doubted Applicants' asserted utility, regardless of the nature of the mechanism that caused these observed reductions in tumor weight.

The Examiner's reliance upon Ponzio *et al.* to reject Applicants' instant invention is therefore misplaced because the findings of Ponzio *et al.* would not cause one of ordinary skill in the art reasonably to doubt the utility of Applicants' present invention. Specifically, the Examiner states that "[a]s for the lower LN weight observed for SJL/RCS mice who received the soluble lymphotoxin beta receptor, one in the art might look for explanation elsewhere because Ponzio et al . . . teach unlike other tumor growth, immunosuppression have an adverse effect to transplantability of RCS." Applicants reiterate their prior objection to the breadth with which the Examiner has interpreted Ponzio et al. (IDS, 1986, Intern. Rev. Immunol., vol. 1, pages 273-301). Ponzio *et al.* teaches the use of SJL mice to determine the effect of γ-irradiation and cyclophosphamide administration on transplantation of spontaneous reticulum cell sarcomas (RCS). Administration of γ-irradiation or cyclophosphamide to SJL mice was not only found to prevent transplantability of primary RCS, but also to diminish the growth of established transplantable RCS lines. Thus, the conclusions of Ponzio *et al.* are derived from studies of γ-irradiated or cyclophosphamide-treated SJL/RCS mice. In contrast, Applicants' data in the instant specification establish treatment of SJL/RCS mice using soluble LTβR agents. A skilled artisan would therefore not reasonably doubt the utility of Applicants' claimed administration of a soluble LTβR agent (a much more targeted and subtle treatment than γ-irradiation or cyclophosphamide) as a treatment for follicular lymphoma based on the findings of Ponzio *et al.*

Additionally, the Examiner's reliance on the '351 patent and the Gommerman review are inappropriate, as neither reference provides objective evidence that would cause

one of ordinary skill in the art to doubt the asserted utility of a soluble LTβR agent as a treatment for follicular lymphoma. Specifically, Applicants' present results establishing soluble LTβR agent-mediated treatment of follicular lymphoma are directly relevant to the claimed invention in comparison with the data of the '351 patent upon which the Examiner has relied. Similarly, the Gommerman review states that LTβR-Ig can cause certain architectural and functional changes in a lymph node, yet Applicants' conclusion that LTβR-Ig can be used to treat follicular lymphoma is founded upon Applicants' observation of a five- to ten-fold reduction in lymph node weight following repeated LTβR-Ig treatments ***in an art-recognized follicular lymphoma model***. Having observed such dramatic lymph node weight reductions in SJL/RCS model mice, one of ordinary skill in the art would reasonably have shared Applicants' conclusion that LTβR-Ig treatment inhibited RCS tumor growth, even prescient of the Gommerman review's contents. Applicants additionally traverse the Examiner's reliance upon the Gommerman review as improper, as the Gommerman review was published more than five years subsequent to the priority date of the present invention, and therefore cannot be relied upon as objective evidence in support of the Examiner's position that one of ordinary skill in the art reasonably would have doubted the asserted utility of the instant invention. Applicants submit that the Gommerman review was introduced in Applicants' response of June 22, 2004, for the express purpose of clarifying the distinction between LT-α and LT-α/β heteromer ("surface LT") signaling to the Examiner.

Applicants also submit that the Examiner has improperly focused on an understanding of the mechanism underlying Applicants' results which has no bearing on the ability of one of ordinary skill in the art to practice the claimed invention. Applicants respectfully submit that "[a]n inventor need not comprehend the scientific principles behind the invention" and that "[t]he inventor's theory or belief as to how the invention works is not a necessary element to satisfy the enablement requirement." *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). Thus, the disclosure of the precise mechanism of soluble LTβR agent activity in producing decreased lymph node volume in the SJL/RCS mouse model of follicular lymphoma is not a prerequisite to the patentability of the present invention. A skilled artisan must be able to practice the methods of the invention by treating follicular lymphoma in a subject through administration of a soluble LTβR agent of the invention. A skilled artisan would be able to do

so, based on the teachings in Applicants' specification and the knowledge of one skilled in the art.

Applicants submit that the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed methods without need to perform an undue amount of experimentation. Applicants describe treatment of mice with a soluble LTβR agent, which results in lower tumor volume in comparison to untreated control mice. Applicants use SJL/RCS mice, an established murine model system used to evaluate tumor treatment, as these mice normally develop tumors. Thus, Applicants have demonstrated reduction in tumor volume using soluble LTβR in a relevant mouse model through working examples. Quite simply, Applicants have shown that the claimed methods work and provide sufficient guidance for a skilled person to practice the claimed methods. Applicants are not legally required to disclose the precise mechanism of LTβR-Ig activity that caused reduced lymph node weights in the art-recognized follicular lymphoma model employed, yet the Examiner has improperly rejected claims 20, 24-26 and 31-33 and 36-53 for want of such disclosure. The Examiner additionally has failed to provide objective evidence that one of ordinary skill in the art would reasonably have doubted the presently claimed use of soluble LTβR for treating follicular lymphoma in view of Applicants' results. Absent such evidence, the Examiner should therefore withdraw the rejection of claims 20, 24-26 and 31-33 and 36-53 under 35 U.S.C. §112, first paragraph.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. BGNA046CPRCE from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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